

**REMARKS**

Reconsideration of the rejections set forth in the Office Action mailed June 29, 2006, is respectfully requested. Claims 1, 14 and 28 have been amended. These amendments were made for clarification purposes. Therefore, these amendments have been made without the addition of new matter. Claims 1, 7-9, 13, 14, 16-17, 28-32, 34, 36-37, 67, 72-73, 78-80, 87-88, and 90-93 remain pending.

**Claim Objections**

Claims 1 and 14 were rejected for repeating the word “at.” Applicants have amended the claims to specify that an electronic potential is provided “at the at least one microelectrode of the microarray,” wherein “the at least one microelectrode” refers back to the preamble. Therefore, Applicants respectfully request withdrawal of the rejections.

**35 U.S.C. § 112**

Claims 28-32, 34, and 36-37 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. In particular, the Examiner has alleged that the instant claims are unclear because the “claim states that the pH change may result from a change of buffer or a change in electrical potential, and the claim ends with the step of changing the electronic potential.” Applicants have amended the claim to specify that “when an electronic potential is used to alter the pH, the electric potential is applied at a current density of between 50 nA/5000 $\mu$ m<sup>2</sup> and 5  $\mu$ A/5000 $\mu$ m<sup>2</sup> at the at least one electrode for a time period between 30 and

600 seconds.” Therefore, Applicants respectfully request withdrawal of the rejections and reconsideration of the claims as amended.

Art Rejections

Claims 1, 7-9, 13-14, 16, 17, 28-32, 34, 37, 72, 73, 78-80, 87-88, and 92 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Sosnowski et al. (US 2003/0190632A1). Claims 36, 90, 91, and 93 were rejected as allegedly unpatentable over Sosnowski et al. in view of Blackburn et al. (USP 6,767,816). The Examiner has alleged that “R group (succinimidyl ester) which is activated by running an electronic current [] could cause a change in the pH in the overlying solution (page 25, paragraphs 0300, 0304) before reacting with a biomolecule (DNA) (page 25, paragraph 0304).” (Office Action, page 4)

Claims 1 and 14 require that “*R is activated by a chemical transformation caused by a pH change in an overlying solution generated by providing an electronic potential at the at least one microelectrode of the microarray before reacting with the biomolecule.*” Similarly, claim 28 requires that “*R comprises chemical elements requiring activation by a chemical transformation caused by a pH change in an overlying solution.*” Applicants respectfully assert that the succinimidyl ester described in Example 3 of Sosnowski was not activated by a pH change in the overlying buffer solution. In support of this proposition, Applicants submit herewith the Declaration of Michael Heller, PhD., a Professor in the Departments of Bioengineering and Electrical Computer Engineering at the University of California, San Diego, and Co-Founder of Nanogen, Inc. Dr. Heller is also a co-inventor of Sosnowski et al., US 2003/0190632 A1.

Example 3 was performed on an apparatus made up of capillary tubes mounted such that they shared a common upper buffer reservoir and had individual lower buffer reservoirs, each of which contained a platinum wire electrode. (See paragraphs 0299, 0300, and 0304) Each of the upper and lower buffer reservoirs were filled with 0.1 M sodium phosphate, pH 7.4. (See paragraph 0304 and Heller Decl. ¶ 4) The capillaries were prerun for 10 minutes at 0.05 mA and then the capture sequence (ETIOAL) was added and electrophoretic transport was carried out for 2-5 minutes. (See paragraph 0304 and Heller Decl. ¶ 4) The microcapillary tubes were filed with 18-26% polyacrylamide and 1% succinimidyl acrylate. (See paragraphs 0299 and 0304) The 5' amino terminus of the capture sequence reacted with the succinimidyl esters in the capillary tubes to form covalent bonds to associate the capture sequence with a specific capillary. (See Heller Decl. ¶ 5)

Contrary to the Examiner's assertion, the succinimidyl ester was not activated by a pH change in the overlying buffer solution. As explained by Dr. Heller, "[t]he succinimidyl ester is very labile and reacts with primary amines without the need for any pH change to activate the succinimidyl ester. Any pH change would be incidental and would not be the cause of any chemical transformation that activates the succinimidyl ester." (See Heller Decl. ¶ 6) As further support, Dr. Heller explained that the current at which the experiment in Example 3 was run (0.5mA) is too low to create a significant change in the buffer reservoir. (See Heller Decl. ¶ 7(a)) Additionally, the set-up of the device precluded any pH change in the buffer with respect to the succinimidyl ester. As explained by Dr. Heller, "[i]n the device used in Example 3, the top of the capillary tube and the shared common upper buffer reservoir are far removed from the platinum wire electrode located in the individual lower buffer reservoir. Therefore, any pH

change that may occur immediately around the electrode in the lower buffer reservoir would not cause any pH change in the capillary or in the upper buffer reservoir, which is where the reaction between the succinimidyl ester and the capture sequence occurs.” (Heller Decl. ¶ 7(b)) The presence of the separate upper and lower buffer reservoirs ameliorates any potential change or fluctuation in pH with respect to the succinimidyl ester. (See Heller Decl. ¶ 8) Therefore, Sosnowski does not teach or suggest a permeation layer having a functional moiety that “*is activated by a chemical transformation caused by a pH change in an overlying solution,*” as required by the claims.

For all the foregoing reasons, Applicants assert the claims are in condition for allowance. Favorable action on the merits of the claims is therefore earnestly solicited. If any issues remain, please contact Applicants’ undersigned representative at (949) 760-9600. The Commissioner is hereby authorized to charge any additional fees that may be required to Deposit Account No. 50-2862.

Respectfully submitted,  
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